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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,381	09/18/2001	Raymond Bernasconi	4-30868A/C1	1717

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NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,381	BERNASCONI ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 17-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *none* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *060705*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/07/05 has been entered.

Applicant is notified that the amendments put forth on 06/07/05, have been entered in full. Applicant is reminded that the claims are being examined only to the extent that they read on the elected invention, i.e. methods of treating Parkinson's disease.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments and persuasive arguments. The statutes upon which the following rejections are based can be found in the prior Office action.

Rejections:

Claims 4 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, as set forth previously and reiterated below. The specification while being enabling for the art recognized treatment of Alzheimer's disease, does not reasonably provide enablement for methods of treating Parkinson's disease, nor does the specification provide any meaningful use for methods of increasing neurotrophin levels in Parkinson's patients wherein this increase does not provide a treatment of Parkinson's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The specification discloses that $GABA_B$ receptor antagonists have been found to increase the amounts of nerve growth factor (NGF) and brain-derived nerve factor (BDNF). Based on this, the specification makes the speculation that $GABA_B$ receptor antagonists should be useful in the treatment of a variety of neurodegenerative disorders. However, no data of any kind is provided to support this speculation. One of skill in the art appreciates that the variety of disorders listed in the first paragraph of page 5 result from distinct and divergent etiologies, involve disparate cell types and have largely been found to be recalcitrant to treatments, particularly those involving neurodegeneration. Further, $GABA_B$ receptor antagonists have now been well studied in the art, and it would not be predictable that $GABA_B$ receptor antagonists would have any benefit in the treatment of Parkinson's disease. This has been born-out by Zeevalk, GD et al., Experimental Neurology 176(193-202)2002 who found that the $GABA_B$ receptor antagonist Saclofen was without effect on the malonate-induced toxicity of straital dopamine neurons in a rat model of Parkinson's disease (see the last paragraph of page 195). Moreover, Zeevalk, GD et al. review the state of the art and conclude that their

findings were not surprising in view of the prior art, such art being available at the time the instant application was filed, see the middle paragraph of page 198.

Therefore due to the large quantity of experimentation necessary to try to find away to treat disorders other than Alzheimer's disease with a $GABA_B$ receptor antagonist, as taught by Yu et al., if such a way can be found, the lack of direction/guidance presented in the specification regarding which disorders, if any, are amenable to such treatment, the absence of working examples directed to same, the complex nature of the many disparate disease states contemplated by the claims, the contradictory state of the state of the prior art as reviewed by Zeevalk, GD et al and also validated by the same authors, and the breadth of the claims which encompass perhaps the whole spectrum of disparate neurodegenerative disorders, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues that it appears that the basis of the rejection should be under USC 101. This argument has been fully considered but not deemed persuasive. The rejection is based on the make and use requirements of USC 112, first paragraph, see above.

Applicant argues that the specification describes a relationship between administration of GABAB receptor agonists and increases in neurotrophin levels in the brain. And that this relationship would logically extend to a neuroprotective effect in Parkinson's disease. This argument has been fully considered but not deemed persuasive. One skilled in the art of molecular neurobiology and medicine appreciates that what might appear prima facia logical need not translate into reality. As pointed out above regarding Zeevalk, GD et al., it might be logical to conclude, based on Applicant's disclosure, that GABAB receptor antagonists

applied directly to the striatum would be protective of Dopamine neurons, however, Zeevalk found that they were not. While applicant is not required to provide a working example of the invention, it is not enough to simply make a speculation and then invite one of skill in the art to try to validate it, particularly when the speculation is contrary to what is known in the art. In *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

See also, Genentech, Inc. v. Novo Nordisk Inc, wherein the court held that "Tossing out the mere germ of an idea does not constitute enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech, Inc. v. Novo Nordisk Inc., 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997).

Applicant argues that the prior art, Siegel et al. and Bradford et al., recognize that neurotrophins are potential therapeutics target for Alzheimer's and Parkinson's disease. This argument has been fully considered but not deemed persuasive. The art recognizes many potential treatments for Alzheimer's and Parkinson's disease, yet these disorders are among the most recalcitrant disorders known.

Applicant further argues that Bradford teach that neurotrophins could be useful as thereaputic agents if they could be delivered to the target sites in the brain and that the

present invention over comes this problem. This argument has been fully considered but not deemed persuasive. There is no indication in the specification that administration of these GABAB antagonist deliver the appropriate neurotrophins to the appropriate targets in the brain for treating Parkinson's disease. Applicant did not even look for an effect in the substantia nigra or striatum. Moreover, Zeevalk, GD et al. administered a GABAB antagonist directly to the striatum and found no protective effect.

Applicant argues that Applicant is not required to provide clinical data for the treatment of Parkinson's disease, rather Applicant's have used a rat model. This argument has been fully considered but not deemed persuasive. There is no requirement for clinical trials and nor has Applicant used a rat model of Parkinson's disease. Zeevalk, GD et al used a rat model of Parkinson's disease and found that administration of a GABAB antagonist had no protective effect.

Applicant argues that Zeevalk, GD et al. has not "done the experiment", because they administered the GABAB antagonist to the striatum and not the substantia nigra nor systemically. Additionally, citing prior art, Applicant argues that the striatum and the substantia nigra are different brain regions and that administration to the substantia nigra might produce a protective effect. This argument has been fully considered but not deemed persuasive. Again it should be pointed out that Applicant has not looked at the effect of systemic administration on either the striatum or substantia nigra. While it may be that administration to the substantia nigra would be beneficial, it is still anyone's guess. Further, one might expect that if GABAB antagonists induce neurotrophins in all regions of the CNS, as applicant apparently suggests, then the neurotrophins produced in

the striatum would be expected to reach the substantia nigra through retrograde axonal transport, as the striatum receives substaintial input from the substantia nigra and neurotrophins are known to operate by retrograde axonal transport from a target region (e.g. straitum) to the cell body (e.g. the substantia nigra), see Fig 3.1 of Bradford et al.

Applicant's request for an interview is noted. Applicant should contact the examiner by telephone to schedule an interview.

Conclusion

This application contains claims 4 and 24 encompass subject matter drawn to a non-elected invention, i.e. ALS and stress-induced neurodegeneration, A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.
Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

ELIZABETH KEMMERER
PRIMARY EXAMINER

August 20, 2005